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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,888	09/29/2003	Ellen W. Evans	OC01600 US	1648

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PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

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02/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/673,888	EVANS ET AL.	
	Examiner	Art Unit	
	ROY P. ISSAC	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6-8,17-21,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6-8,17-21,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/07/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicant's amendment/ remarks/ response filed 12/07/07, wherein claims 9-16 and 22-29 have been cancelled and claim 17 have been amended, and claims 30 and 31 are newly submitted.

Rejections Withdrawn

In view of the cancellation of claims 9-16 and 22-29, all rejections made with respect to claims 9-16 and 22-29 in the previous office action are withdrawn.

The rejection of claim 18 under section 112, first paragraph for lack of written description is withdrawn since the claim was filed as a preliminary amendment with the non-provisional application.

In view of the amendments to claim 17 wherein the improper antecedent basis was removed overcomes the rejection of claim 17 under section 112, second paragraph.

The following are new or modified rejections necessitated by Applicant's amendment filed 12/07/07, wherein the limitations in pending claims 17 as amended now have been changed and claims 30 and 31 are newly submitted. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, mailed 08/07/07, have been modified and are listed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to the method for the treatment of disorders associated with calcium homeostasis. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The claimed invention is a therapeutic method for preventing or treating a disorder of calcium homeostasis.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The breadth of the claims and the amount of direction or guidance presented:

The claims are directed to six particular diseases with varying etiology. For example familial benign hypocalciuric hypercalcemia is a syndrome of lifelong hypercalcemia inherited as an autosomal dominant trait. (Heath et. al. West J. Med. 1994, 160, 554-561; Of record). On the other hand, Hypercalcemia of malignancy is an oncologic emergency that is associated with a median life expectancy of approximately 30 days. (Pearl et. al., Oncology update, 1996, 163-166). The etiology of hypercalcemia of malignancy is multifactorial with at least four putative mechanisms, and mechanism varies with tumor type and stage of disease. (Pearl et.al., Page 163, Column 2). First, local bone resorbing factors are though to mediate the hypercalcemial observed in hematologic malignancies. Second, bony metases from solid tumors produce localized osteolysis that may result in hypercalcemia of malignancy. Third, parathyroid hormone related proteins secreted by tumor mimic the renal effects of parathyroid hormone and impair hormone excretion. The experiments herein describe the administration of compound of Formula I to normal rats without hypercalcemia. The administration results in increased excretion of calcium and a lowering of PTH levels. From the increased excretion level and lower PTH level, the results herein seems to follow the third pathway. However, it is not clear form the disclosure how the increased excretion is achieved. Furthermore, there is no indication as to how or whether the

compounds of claim 18 can effectively treat a genetic disorder or hypercalcemia of malignancy caused by one of the other pathways.

The amount of direction or guidance presented and the presence or absence of working examples:

The examples 1-2 relates to the study of toxicity of the compound of Formula I. Note that the compound of Formula I is a well-known pharmaceutical in clinical use. Example 2 involves the microscopic evaluation of rats that were given the compound of formula I, which shows that the parathyroid glands are affected by the administration of said compound. However, the examples do not indicate that the rats were suffering from any particular disorders associated with calcium homeostasis. Furthermore, the diseases listed has very diverse etiology. For example, osteoporosis is a disease of progressive decrease in bone density. It is not clear how increasing the calcium excretion level will help reduce the loss of calcium density of the skeletal system. One of skill in the art would think increasing the calcium excretion would have the opposite effect of speeding up the progression of osteoporosis. In fact, calcium supplements are recommended for those at risk for osteoporosis. (Merck Manual of Medical Information, Home Ed. Pages 238-240;Of record). While osteoporosis is a slow progressing disease that reduce bone density, hypercalcemia of malignancy is a fast setting condition associated with many of the commonly occurring cancers. Hypercalcemia of malignancy is considered an oncologic emergency that is associated with a median life expectancy of 30 days. (Pearl et. al., Oncology Update, 1996, Pages 163-166; Of record). It is conceivable that in such an emergency situation, lowering calcium levels

with excretion is helpful, only if it is not achieved by increasing bone resorption. The examples disclosed herein shows that calcium excretion is increased. However, the specification doesn't address whether such excretion is achieved at the expense of lowering bone density. If the increase in calcium excretions is achieved by extracting calcium from bone mass, it is certainly the opposite of what a patient with osteoporosis would hope to achieve.

On the other hand, familial benign hypocalciuric hypercalcemia is a syndrome of lifelong hypercalcemia inherited as an autosomal dominant trait. (Heath et. al. West J. Med. 1994, 160, 554-561;Of record). Hypercalcemia of malignancy is an oncologic emergency that is associated with a median life expectancy of approximately 30 days. (Pearl et. al., Oncology update, 1996, 163-166). The etiology of hypercalcemia of malignancy is multifactorial with at least four putative mechanisms, and mechanism varies with tumor type and stage of disease. (Pearl et.al., Page 163, Column 2). First, local bone resorbing factors are though to mediate the hypercalcemial observed in hematologic malignancies. Second, bony metases from solid tumors produce localized osteolysis that may result in hypercalcemia of malignancy. Third, parathyroid hormone related proteins secreted by tumor mimic the renal effects of parathyroid hormone and impair hormone excretion.

There are no examples of the synthesis of either of the compounds of claim 18, or any compounds with a substituent on the seven membered ring similar to compounds of claim 18. There are no examples of the use of compounds of claim 18 for the treatment of any particular disease. The lack of working examples is a critical and

crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

The predictability or lack thereof in the art and the quantity of experimentation necessary:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation encompasses thousands of compositions with varying effects and unknown side effects. As such, each composition will need to be individually evaluated for activity.

The specification as originally filed does not describe any methods of making or using compounds of claim 18. Since the compounds of claim 18, even though retains the structural tricyclic core do have additional functionalities, which would not have been readily apparent to one of skill in the art. The provisional application from which this application depends does not claim nor describe the compounds of claim 18. See above rejections for the analysis of Wands factors. In view of the wands analysis of unpredictability in the pharmaceutical arts, lack of any working examples of either of the compounds of claim 18 for making or using the compounds as claimed, the diverse etiology of the various disease conditions claimed, and the complete lack of guidance to make and use the compounds of claim 18, one of skill in the art would have to commit

to substantial research and development including participation by principal scientists, clinicians and a vast number of support staff to design organic synthetic methodology as well as to test compounds for physiological and biochemical properties. Therefore, in view of the *Wands* factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation***.

Response to Arguments

Applicant's arguments filed 12/07/07 have been fully considered but they are not persuasive. Applicants argue that the two compounds of claim 18 could have been prepared by one of skill in the art without undue experimentation. Applicants submit that the compounds of claim 18 could have been used in the same manner in which compounds 1-81 could have been used. Applicants point to PCT application no WO2005/014577 to provide examples for the synthesis of these compounds. To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. The cited reference has a publication date after the filing of the instant application. The application must be enabled as of its filing date. For new compounds, method of synthesis must be present even if not claimed. Synthesis methods for new intermediates must also be present. (*Lilly v. Barr*, 55 USPQ2d 1609, Fed. Cir. 2000). Furthermore, where applicants define the invention by Markush group, applicant must enable one of skilled in the art to make and use at least one composition employing each member of the Markush group. *In re*

Fouche, 169 U.S. P.Q. 429, 434 (C.C.P.A. 1971). The compounds applicants have pointed to in the specification, compounds 1-81, lacks the particular substituents as of claim 18.

Applicants further notes that the examiner has indicated in a prior office action that the claims are enabled. However, further review of the specification indicated that the compounds of claim 18 were only presented as a preliminary amendment in claim 18. The specification does not provide any methods for preparing these compounds. Furthermore, the two compounds of claim 18 are structurally dissimilar to the compounds described in the specification since the compounds in the specification lack key substituents to the seven membered ring. As such, a closer look at the record by the examiner revealed that the specification lacks enabling disclosure to make and use these two compounds. There is nothing unusual, certainly, about an examiner changing his view point, as to the patentability of claims as the prosecution of case progresses, and, so long as the rules of Patent Office practice are duly complied with, an applicant has no legal ground for complaint because of such change in view. (*In re Ruschig* 154 USPQ 118, (C.C.P.A 1967), See also, *In Re Ellis*, 31 USPQ 380; *In Re Becker*, 40 USPQ 624). The rejection under section 112, first paragraph is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims herein appear to have trademarks/abbreviation (AMG 073, NPS 467 for example) in the claims. Applicant is advised that full chemical names should be used in claims. Under 35 U.S.C 112 it is improper to use an acronym without defining it first within claims. Where a trademark or trade name or abbreviation is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C 112, second paragraph. See *Ex parte Simpson,* 218 USPQ (Bd. App. 1982). Appropriate correction is required.

Response to Arguments

Applicants have not addressed the above rejection in their response dated 12/07/07. The rejection is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-3, 6-8, 17-21 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et. al. (Of Record) in view of Pearl et. al. (Oncology Update,

1996, 3(5), 1996, 163-166; PTO-892) further in view of (Merck Manual of Diagnostics, Home Ed. 1997, Pages 738-739; Of record)

Doll et. al. teaches each of the compounds 1-81 of the instant application for the treatment of several cancers. Tricyclic compounds of Formulae 1-81 of the instant application are disclosed. (Doll et. al, WO/97/23478; Page 15, lines 1-15 and; Page 2 line 10 to Page 13, line10). Doll et. al. further discloses the use of said compounds in patients and with pharmaceutically acceptable carriers. (Page 115, line 5 to Page 116 line 5). Doll et. al further discloses the use of compounds of Formulae 1-81 for the treatment of a variety of cancers that account for majority of the commonly occurring cancers including lung cancer, pancreatic cancers, thyroid follicular cancer, colon cancers, myeloid leukemias, bladder cancer, myelodysplastic syndrome, epidermal cancers, prostate cancers and breast cancers. (Page 116, lines 4-10; Page 15, last paragraph to Page 16, first pargraph). Doll et. al. further discloses tablet formation. (Page 88).

Doll et. al. does not expressly disclose the use of compounds of formulae 1-81 for the treatment of malignancy associated hypercalcemia or humoral hypercalcemia of malignancy or a combination of one of the compounds of formulae 1-81 with another compound.

Pearl et. al. discloses that hypercalcemia of malignancy is an oncologic emergency that occurs in nearly 50% of patients with multiple myeloma or breast cancer. (Page 163, Column 1, Paragraph 2). Patients with lung and epidermoid cancers also have a significant incidence of hypercalcemia. For two reasons, a large

portion of patients with hypercalcemia of malignancy are expected to be treated with compounds of Formulae 1-81 based on the disclosure of Doll et. al. One, Doll et .al. discloses the use of compounds of formulae 1-81 for the treatment of a large number of cancers, particularly ones that have high incidences of hypercalcemia of malignancy. Two, hypercalcemia of malignancy can only occur in patients with cancers, and Doll et. al. discloses the use of compounds of Formulae 1-81 for the treatment of a large number of commonly occurring cancers. Pearl et. al. further disclose several therapies for the treatment of hypercalcemia of malignancy such as saline rehydration and the use of calcitonin. (Page 164, Columns 2-3).

Merck Manual of Diagnostics,notes that people with cancer often have hypercalcemia. A variety of cancers including lung and kidney cancers are disclosed to often result in hypercalcemia. (Page 739, Column 1, paragraph 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat patients with hypercalcemia of malignancy with a compound of formulae 1-81 since hypercalcemia of malignancy is often present in breast and lung cancers as well as in cancers in general and Doll et. al. discloses the use of compounds of Formulae 1-81 for the treatment of breast and lung cancers as well as a variety of cancers that are commonly occurring. Since a large portion of patients with hypercalcemia of malignancy are expected to receive compounds of formula A as treatment for cancer the benefit of lowering calcium levels is achieved by the same or similar patient population. The patient population in Doll et al. is deemed to anticipate, overlap, or coincide the patient in this claimed invention, in need of such a

treatment of hyperparathyroidism, malignancy-associated hypercalcemia or humoral hypercalcemia of malignancy.

Furthermore, it would have been obvious to one of ordinary skill in the art to combine two treatment regiments such as commonly used drug calcitonin or 1, 25-dihydrovitamin D to achieve beneficial cumulative effects in the treatment of hypercalcemia of malignancy. It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Therefore, one of ordinary skill in the art would have reasonably expected that the benefit of lowering calcium levels in a patient with hypercalcemia of malignancy would have occurred from the treatment of a patient with cancer with a compound of formulae 1-81. Furthermore, one of ordinary skill in the art would have expected that a composition comprising one compounds of formulae 1-81 in combination with calcitonin would have had beneficial cumulative effects in the treatment of a patient with hpercalcemia of malignancy.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 12/07/07 have been fully considered but they are not persuasive. Applicants argue that no reason exist for a person of ordinary skill in the field to combine the teachings of references cited. Applicants further argue that a practitioner would not have had any reasonable expectation of success in using any of compounds 1-81 for the treatment of calcium homeostasis. As noted in the previous office action, for two reasons, a large portion of patients with hypercalcemia of malignancy are expected to be treated with compounds of Formulae 1-81 based on the disclosure of Doll et. al. One, Doll et .al. discloses the use of compounds of formulae 1-81 for the treatment of a large number of cancers, particularly ones that have high incidences of hypercalcemia of malignancy. Two, hypercalcemia of malignancy can only occur in patients with cancers, and Doll et. al. discloses the use of compounds of Formulae 1-81 for the treatment of a large number of commonly occurring cancers. Pearl et. al. further disclose several therapies for the treatment of hypercalcemia of malignancy such as saline rehydration and the use of calcitonin. (Page 164, Columns 2-3). Since a large portion of patients with hypercalcemia of malignancy are expected to receive compounds of formula A as treatment for cancer the benefit of lowering calcium levels is achieved by the same or similar patient population. The patient population in Doll et al. is deemed to anticipate, overlap, or coincide the patient in this claimed invention, in need of such a treatment of hyperparathyroidism, malignancy-associated hypercalcemia or humoral hypercalcemia of malignancy. The rejection under section 103(a) is still deemed proper and is adhered to.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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